RE: EFFICACY AND SAFETY OF WELLBUTRIN XL® COMPARED WITH OTHER ANTIDEPRESSANTS

SUMMARY

- Wellbutrin XL® (bupropion HCl extended-release tablets) is a once-daily formulation of bupropion indicated for the treatment of major depressive disorder (MDD) in adults aged 18 and older.
- *Wellbutrin XL* and Lexapro® (escitalopram oxalate, Forest Labs) have been compared with respect to antidepressant efficacy, effects on sexual functioning, and safety in 2 randomized, double-blind, placebo-controlled trials.
- Wellbutrin SR® (bupropion HCl) Sustained-Release Tablets and Zoloft® (sertraline hydrochloride, Pfizer) have been proven comparably effective in treating depression and accompanying symptoms of anxiety in 3 double-blind, randomized, multicenter studies.
- *Wellbutrin SR* and Prozac® (fluoxetine HCl, Eli Lilly and Company) have been compared with respect to antidepressant efficacy, effects on sexual functioning, and safety in 2 randomized, double-blind, placebo-controlled clinical trials.
- A randomized, double-blind, controlled, clinical trial comparing Wellbutrin® (bupropion HCl) Tablets and fluoxetine found both to be similarly efficacious for the treatment of depression and accompanying symptoms of anxiety. Treatment-emergent adverse events were also similar.
- *Wellbutrin SR* and Paxil® (paroxetine HCl, GlaxoSmithKline) were shown to be comparably effective in treating depression and accompanying symptoms of anxiety in elderly depressed patients in a double-blind, randomized, multicenter study.
- *Wellbutrin* has also been compared to various tricyclic antidepressants (TCAs) in double-blinded studies.

Some information contained in this response may be outside the approved Prescribing Information for *Wellbutrin XL*. This response is not intended to offer recommendations for administering *Wellbutrin XL* in a manner inconsistent with its approved labeling. In order for GlaxoSmithKline to monitor the safety of *Wellbutrin XL*, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the Prescribing Information for *Wellbutrin XL*.

BACKGROUND

Studies have demonstrated similar bioavailability of the immediate-release and the extended-release formulations of bupropion under steady-state conditions (1).The bioavailability (both peak plasma concentration and extent of absorption) of *Wellbutrin XL* 300 mg once daily was similar to that of 100 mg 3 times daily of *Wellbutrin* for parent drug and metabolites. Similar studies have also demonstrated the bioequivalence of *Wellbutrin XL* and *Wellbutrin SR*. Based on bioequivalence, *Wellbutrin XL* offers similar efficacy and tolerability as other formulations of bupropion.

Table: Comparative Clinical Trials with Bupropion for the Treatment of Major Depressive Disorder

Duration	Study Design	Treatments	Inclusion/ Exclusion Criteria	Endpoints	Results
Bupropion vs. Escitalopram					
8-wk treatment phase (2)	• Placebo-controlled • Double-blind • Randomized • N=410	***Wellbutrin XL*** • Initial dose 150 mg/day • Max dose 450 mg/day (in divided doses) **Escitalopram** • Initial dose 10 mg/day • Max dose 20 mg/day	**Inclusion Criteria** • Males & females (≥18yrs) • Baseline HAMD-17 ≥19 • Current major depressive episode of 3-24 mns duration • Normal orgasmic function & willing to discuss sexual activity **Exclusion Criteria** • Arousal or orgasm dysfunction at screening or randomization • Hx of no response to 2 or more treatments for any depressive episode within 2 yrs • Prior treatment with bupropion within 3 mns • Hx of psychoactive drug including SSRIs within 2 wks (4 wks for fluoxetine) • Hx of MAOI use • Predisposition to seizure • Hx or current diagnosis of anorexia nervosa or bulimia • Hx unstable medical disorder • Actively suicidal • Pregnant or lactating	**Efficacy** (N=388) • Δ in HAMD-17 • HAD • CGI-I **Sexual Functioning** • Orgasm dysfunction • CSFQ • Sexual desire • Sexual arousal • Patient satisfaction **Safety** (N=410) • Weight • Vital Signs • AE Reports	• Efficacy - no statistical differences between *Wellbutrin XL* and escitalopram for any given measure • No statistically significant differences in HAMD scores among the 3-treatment groups at all time points • Orgasm dysfunction - significantly higher for escitalopram vs. *Wellbutrin XL* from day 7 through the last treatment day (day 56) • Sexual functioning - Δ in CSFQ total scores from baseline to week 8 were significantly reduced for escitalopram vs. *Wellbutrin XL* or placebo • Patient satisfaction – overall sexual functioning at week 8 less in escitalopram-treated patients (74%) vs. *Wellbutrin XL* (88%, $P < 0.05$) vs placebo (88%, $P < 0.05$) • AEs reported in ≥ 5% of patients & 1.5X placebo: - Escitalopram - fatigue, dizziness, flatulence, upper respiratory tract infection, yawning - *Wellbutrin XL* - dry mouth, insomnia, dizziness, constipation • Discontinuation due to AEs - Escitalopram (3%), Placebo (5%), *Wellbutrin XL* (10%) • No reports of seizure for any treatment • Suicidality - Escitalopram – no reports - *Wellbutrin XL* – no reports - Placebo – self-mutilation, intentional self injury (1 report each)
8-wk treatment phase (3)	• Placebo-controlled • Double-blind • Randomized • N=420	***Wellbutrin XL*** • Initial dose 150 mg/day • Max dose 450 mg/day (in divided doses) **Escitalopram** • Initial dose 10 mg/day • Max dose 20 mg/day	**Inclusion Criteria** • Same as previous **Exclusion Criteria** • Sane as previous	**Efficacy** (N=397) • Δ in HAMD-17 • HAD • CGI-I **Sexual Functioning** • Orgasm dysfunction • CSFQ • Sexual desire • Sexual arousal • Patient satisfaction **Safety** (N=420) • Weight • Vital Signs • AE Reports	• Efficacy - no statistical differences between results for *Wellbutrin XL* and escitalopram for any given measure • No statistically significant differences in HAMD scores between *Wellbutrin XL* and placebo at all time points • Remission rates with *Wellbutrin XL* and escitalopram were significantly greater than placebo • Orgasm dysfunction - significantly higher for escitalopram vs. *Wellbutrin XL* from day 7 through the last treatment day (day 56) • Sexual functioning - CSFQ scores significantly reduced for escitalopram vs. *Wellbutrin XL* or placebo • Patient satisfaction – overall sexual functioning at week less in escitalopram-treated patients (75%) vs. *Wellbutrin XL* (84%) vs. placebo (91%, $P < 0.05$) • AEs reported in ≥ 5% of patients & 1.5X placebo: - Escitalopram – nausea, dry mouth, insomnia, diarrhea, ↓'d appetite, nasopharyngitis, somnolence, yawning - *Wellbutrin XL* – nausea, dry mouth, insomnia, constipation,

Duration	Study Design	Treatments	Inclusion/ Exclusion Criteria	Endpoints	Results
					nasopharyngitis, irritability, anxiety • Discontinuation due to AEs - Escitalopram (5%), Placebo (5%), *Wellbutrin XL* (3%) • No reports of seizure for any treatment • Suicidality - Escitalopram – suicidal ideation (3 reports) - *Wellbutrin XL* – no reports - Placebo – suicidal ideation (1 report)
Bupropion vs. Sertraline					
8-wk treatment phase (4)	• Placebo-controlled • Double-blind • Randomized • Multicenter • N=348	***Wellbutrin SR*** • Initial dose 150 mg/day • Max dose 400 mg/day **Sertraline** • Initial dose 50 mg/day • Max dose 200 mg/day **Placebo**	**Inclusion Criteria** • Males & females (≥18yrs) with moderate/severe depression • Recurrent major depressive episode of 2-24 mns duration • 21-item HAMD score of ≥18 • Sexually active & in a stable relationship with normal sexual functioning & activity that could lead to orgasm at least once q 2wks **Exclusion Criteria** • Predisposition to seizure or taking meds that could lower seizure threshold • Hx or current diagnosis of anorexia nervosa or bulimia • Prior treatment with bupropion or sertraline • Hx of psychoactive drug within 1 wk (2 wks for MAOI or protriptyline & 4 wks for fluoxetine) • Hx of alcohol/substance abuse in past yr • Actively suicidal • Pregnant, lactating or unwilling to take contraceptives	**Efficacy** • HAMD • HAMA • CGI-I • CGI-S **Sexual Functioning** • Sexual desire • Sexual arousal • Orgasmic dysfunction • Premature ejaculation (men only) • Patient satisfaction **Safety** • AEs, potentially drug related or not, were elicited with a standard verbal probe procedure • Vital signs • Weight	• *Wellbutrin SR* and sertraline comparably effective in treating depression and related symptoms of anxiety; although placebo also demonstrated comparable efficacy in treating depression-related anxiety • Mean decreases in HAMD, HAMA, CGI-I, and CGI-S scores were similar for both active treatments at all time-points throughout the study • Onset of activity similar for *Wellbutrin SR* and sertraline; no between-group differences on any of the efficacy scales on any treatment day • Orgasm function significantly impaired in sertraline-treated patients from the first week of treatment through the last day of treatment ($P < 0.005$ sertraline vs. *Wellbutrin SR* and placebo) • Significantly more patients reported worsened sexual functioning during treatment with sertraline than during treatment with *Wellbutrin SR* or placebo from the first week of treatment through the last day of treatment ($P < 0.005$ sertraline vs. *Wellbutrin SR* and placebo) • AEs reported in ≥10% of patients: -Sertraline - headache, nausea, diarrhea, insomnia, somnolence, dry mouth -*Wellbutrin SR* - headache, nausea, insomnia, dry mouth
8-wk treatment phase (5)	• Placebo-controlled • Double-blind • Randomized • Multicenter • N=344	***Wellbutrin SR*** • Initial dose 150 mg/day • Max dose 400 mg/day **Sertraline** • Initial dose 50 mg/day • Max dose 200 mg/day **Placebo**	**Inclusion Criteria** • Same as previous **Exclusion Criteria** • Same as previous	• Same as previous	• *Wellbutrin SR* and sertraline comparably effective in treating depression and related symptoms of anxiety; although placebo also demonstrated comparable efficacy in treating depression-related anxiety • Mean decreases in HAMD, HAMA, CGI-I, and CGI-S scores were similar for both groups at all time-points throughout the study • Onset of efficacy similar for *Wellbutrin SR* and sertraline; no between-group differences on any of the efficacy scales on any treatment day • Orgasm function significantly impaired in sertraline-treated patients from the first week of treatment through the last day of

Duration	Study Design	Treatments	Inclusion/ Exclusion Criteria	Endpoints	Results
					treatment ($P < 0.005$ sertraline vs. *Wellbutrin SR* and placebo) • Significantly more patients reported worsened sexual functioning during treatment with sertraline than during treatment with *Wellbutrin SR* or placebo from the first week of treatment through the last day of treatment ($P < 0.005$ sertraline vs. *Wellbutrin SR* and placebo) • AEs reported in ≥10% of patients: -Sertraline - headache, nausea, diarrhea, dyspepsia, insomnia, rhinitis, dry mouth -*Wellbutrin SR* - headache, nausea, diarrhea, insomnia, agitation, dry mouth
16-wk treatment phase (6,7)	• Double-blind • Randomized • Multicenter • N=248	***Wellbutrin SR*** • Initial dose 100 mg/day • Max dose 300 mg/day **Sertraline** • Initial dose 50 mg/day • Max dose 200 mg/day	**Inclusion Criteria** • Males & females (≥18 yrs) with MDD • Recurrent major depressive episode of 1-24 mns duration • Sexually active & in a stable relationship with normal sexual functioning **Exclusion Criteria** • Predisposition to seizure • Hx or current diagnosis of anorexia nervosa or bulimia • Prior treatment with bupropion or sertraline • Hx of psychoactive drug within 1 wk (2 wks for MAOI or protriptyline & 4 wks for fluoxetine) • Actively suicidal • Pregnant or lactating	**Efficacy** • HAMD • HAMA • CGI-I • CGI-S **Sexual Functioning** • Organism functioning **Safety** • AEs, potentially drug related or not, were elicited with a standard verbal probe procedure	• *Wellbutrin SR* and sertraline were comparably effective in treating depression and related symptoms of anxiety • Mean decreases in HAMD, HAMA, CGI-I, and CGI-S scores were similar for both groups at all time-points throughout the study • Onset of efficacy similar for *Wellbutrin SR* and sertraline; no between-group differences were observed on any of the efficacy scales on any treatment day • Sexual function, orgasm, and sexual arousal were significantly impaired in sertraline-treated patients from day 7 through the last treatment day (day 112) • Patients with orgasm delay and/or failure at day 112: - Sertraline - 44% of males and 33% of females - *Wellbutrin SR* - 8% of males and 5% of females • AEs reported in ≥10% of patients: - Sertraline - headache, nausea, diarrhea, insomnia, somnolence, dry mouth, anxiety, sweating - *Wellbutrin SR* - headache, nausea, insomnia, dry mouth, flu
Bupropion vs. Fluoxetine					
8-wk treatment phase (8)	• Placebo-controlled • Double-blind • Randomized • Multicenter • N=456	***Wellbutrin SR*** • Initial dose 150 mg/day • Max dose 400 mg/day **Fluoxetine** • Initial dose 20 mg/day • Max dose 60 mg/day **Placebo**	**Inclusion Criteria** • Males & females (≥18 yrs) with moderate/severe depression • 21-item HAMD score of ≥20 • Recurrent major depressive episode of 2-24 mns duration • Sexually active & in a stable relationship with normal sexual functioning that could lead to orgasm at least once q 2 wks **Exclusion Criteria** • Predisposition to seizure or taking meds that could lower seizure threshold • Hx or current diagnosis of anorexia nervosa or bulimia	**Efficacy** • HAMD **Sexual Functioning** • Sexual desire • Sexual arousal • Orgasmic dysfunction • Patient satisfaction **Safety** • AEs, potentially drug related or not, were elicited with a standard verbal probe procedure • Vital signs	• *Wellbutrin SR* and fluoxetine comparably effective in treating depression • No statistically significant differences in HAMD scores among the 3 treatment groups at all time points • The mean total HAMD score was lower at week 8 with *Wellbutrin SR* compared with placebo ($P < 0.05$) • A significantly higher percentage of patients achieved prospectively defined remission (HAMD score ≤8) at week 8 study endpoint with *Wellbutrin SR* (47%) compared with placebo (32%) ($P < 0.05$) • Orgasm function significantly impaired in fluoxetine-treated patients from day 14 of treatment through the last treatment day ($P < 0.001$ fluoxetine vs. *Wellbutrin SR* and placebo) • Significantly more patients reported worsened sexual functioning during treatment with fluoxetine than during treatment with *Wellbutrin SR* or placebo from treatment day 14 through the last

Duration	Study Design	Treatments	Inclusion/ Exclusion Criteria	Endpoints	Results
			• Prior treatment with bupropion or fluoxetine • Hx of psychoactive drug within 1 wk (2 wks for MAOI or protriptyline & 4 wks for any investigational drug) • Hx of non-response to antidepressants • Alcohol/substance abuse in past yr • Actively suicidal • Pregnant, lactating or unwilling to take contraceptives	• Weight	treatment day ($P < 0.001$ fluoxetine vs. *Wellbutrin SR* and placebo) • AEs reported in >10% of patients: - Fluoxetine – headache, nausea, diarrhea, somnolence, insomnia, agitation, dry mouth - *Wellbutrin SR* – headache, nausea, insomnia, agitation, dry mouth - Placebo- headache, dry mouth, nausea, agitation, insomnia, and diarrhea
8-wk treatment phase (9)	• Placebo-controlled • Double-blind • Randomized • Multicenter • N=467	***Wellbutrin SR*** • Initial dose 150 mg/day • Max dose 400 mg/day **Fluoxetine** • Initial dose 20 mg/day • Max dose 60 mg/day **Placebo**	**Inclusion Criteria** • Same as previous **Exclusion Criteria** • Same as previous	• Same as Previous	• *Wellbutrin SR* and fluoxetine equally effective in treating depression • No statistically significant differences in HAMD scores among 3-teatment groups • Orgasm function significantly impaired in fluoxetine-treated patients from day 14 of treatment through the last treatment day ($P < 0.001$ fluoxetine vs. *Wellbutrin SR* and placebo) • Significantly more patients reported worsened sexual functioning during treatment with fluoxetine than during treatment with *Wellbutrin SR* or placebo from treatment day 14 through the last treatment day ($P < 0.01$ fluoxetine vs. *Wellbutrin SR* and placebo) • AEs reported in >10% of patients: - Fluoxetine – headache, nausea, diarrhea, insomnia, rhinitis, dry mouth - *Wellbutrin SR* – headache, nausea, dizziness, constipation, rhinitis, insomnia, agitation, dry mouth
6-wk treatment phase (10)	• Double-blind • Randomized • Multicenter • N=123	***Wellbutrin*** 225-450 mg/day **Fluoxetine** 20-80 mg/day	**Inclusion Criteria** • Males & females (≥18 yrs) with moderate/severe depression • 21-item HAMD score ≥20 • Current depressive episode of 2-24 mns duration **Exclusion Criteria** • Predisposition to seizure • Hx or current diagnosis of anorexia nervosa or bulimia, hepatic or renal dysfunction, thyroid disorder, or other unstable medical condition • Prior treatment with bupropion or fluoxetine • Psychoactive drug within 1 wk (2 wks for MAOI or protriptyline & 4 wks for investigational drug) • Alcohol or substance abuse • Currently taking tryptophan, warfarin,	**Efficacy** • HAMD • CGI-S • CGI-I • HAMA **Safety** • AEs were elicited with a standard verbal probe procedure • Vital signs • Weight	• Mean decrease in HAMD scores similar for both groups • 37 bupropion patients and 35 fluoxetine patients considered responders based on at least a 50% decrease in HAMD • No significant differences between groups on any scores • Mean decrease of 59% in HAMA scores for both groups • AE profile similar for both groups • Most commonly reported AEs in both groups included dry mouth, headache, insomnia, agitation, tremor, nausea, vomiting, diarrhea, constipation • 6 bupropion patients and 4 fluoxetine patients withdrew due to AEs

Duration	Study Design	Treatments	Inclusion/ Exclusion Criteria	Endpoints	Results
			digoxin, or thyroid meds • Actively suicidal • Pregnant, lactating or unwilling to take contraceptives		
Bupropion vs. Paroxetine					
6-wk treatment phase (11)	• Double-blind • Randomized • Multicenter • N=100	***Wellbutrin SR*** • Initial dose 100 mg/day • Max dose 300 mg/day ***Paxil*** • Initial dose 10 mg/day • Max dose 40 mg/day	**Inclusion Criteria** • Elderly depressed outpatients,(age ≥60) • Recurrent major depressive episode of 2-24 mns duration • 21-item HAMD score of ≥18 **Exclusion Criteria** • Predisposition to seizure or taking meds that could lower seizure threshold • Hx or current diagnosis of anorexia nervosa or bulimia • Hx unstable medical disorder • Hx of MI, uncontrolled HTN, or unstable heart disease within 6 mns • Prior treatment with bupropion or paroxetine • Hx of psychoactive drug within 1 wk (2 wks for MAOI or protriptyline & 4 wks for fluoxetine) • Hx of non-response to antidepressants • Alcohol/ substance abuse within past yr • Actively suicidal	**Efficacy** • HAMD • CGI-S • CGI-I • HAMA **Safety** • AEs, potentially drug related or not, were elicited with a standard verbal probe procedure • Vital signs • Weight	• *Wellbutrin SR* and *Paxil* comparably effective in treating depression and related symptoms of anxiety • Onset of efficacy similar for *Wellbutrin SR* and *Paxil*; no between-group differences on any efficacy scale on any treatment day • AEs reported in ≥10% of patients: - *Paxil* – headache, nausea, dry mouth, dizziness, agitation, diarrhea, insomnia, sedation, constipation - *Wellbutrin SR* - headache, nausea, dry mouth, dizziness, agitation, • Incidence of sedation and diarrhea significantly higher with *Paxil* than with *Wellbutrin SR* • No adverse event occurred significantly more often with *Wellbutrin SR* than *Paxil*
Pooled Analysis of Bupropion vs. SSRIs and Placebo					
Acute phase treatment, ranging from 6-16 wks (12)	**Meta-analysis of 5 studies** • Placebo-controlled • Double-blind • Randomized • N=1332	**Average dose:** ***Wellbutrin*** 345 mg/day ***Wellbutrin SR*** 197-238 mg/day **Sertraline** 114-121 mg/day **Fluoxetine** 26 mg/day ***Paxil*** 22 mg/day	**Inclusion Criteria** • Outpatients with moderate to severe depression • mean age: 36-70 yrs	**Efficacy** • HAMD • CGI-I	• The quantitative results for HAMD and CGI-I scores were similar among all studies • No statistically significant difference was noted among efficacy scores for bupropion or the SSRIs at any time in all studies • General adverse event reports were similar with bupropion and SSRIs • Bupropion was associated with less nausea, diarrhea, somnolence, and sexual dysfunction compared with the SSRIs
Acute phase treatment: • 4 studies were 8 wks • 1 study was 16 wk but analyzed at 8	**Retrospective analysis of 7 studies** • Randomized • Double-blind • Multicenter • 4 placebo-	**Daily doses** ***Wellbutrin/ Wellbutrin SR*** 100-450 mg/day **Fluoxetine** 20-60 mg/day **Sertraline**	**Inclusion Criteria** • Outpatients with moderate to severe depression • In 4 studies: normal sexual functioning and sexual activity that could lead to orgasm at least once every 2 wks **Exclusion Criteria**	**Efficacy** • Remission Rates ($HAMD_{17}$ scores ≤ 7) **Sexual Functioning** • Sexual desire • Sexual arousal • Orgasmic	• Remission rates were similar and consistent across trials (*Wellbutrin/ Wellbutrin SR* 47%, SSRIs 47%) and higher than placebo (36%) ($P < 0.01$, bupropion and SSRIs vs. placebo) • Pooled remission rates from the 4 placebo-controlled trials vs the SSRIs (sertraline and fluoxetine) were consistent with the overall analysis (*Wellbutrin SR* 45%, SSRIs 45%, placebo 26%, $P<0.01$) • The 4 active treatments were well-tolerated and showed similar

Duration	Study Design	Treatments	Inclusion/ Exclusion Criteria	Endpoints	Results
wks • 2 studies were 6 wks (13, 14)	controlled • 3 active controlled • N=1975	50-200 mg/day ***Paxil*** 10-40 mg/day	• Hx of bupropion or comparator SSRI within year	dysfunction **Safety**	overall frequencies of AEs • The SSRIs were associated with a greater incidence of orgasmic dysfunction, sexual arousal disorder, and sexual desire disorder compared with bupropion and placebo
Bupropion vs. Other Antidepressants					
6-wk treatment phase (15)	• Double-blind • Randomized • Multicenter • N=115	***Wellbutrin*** 225-450 mg/day **Nortriptyline** 100-150 mg/day	**Inclusion Criteria** • Adults (≥18 yrs) with moderate/severe depression • 21-item HAMD score ≥20 • Recurrent major depressive episode of 1-24 mns duration **Exclusion Criteria** • Predisposition to seizure • Hx or current diagnosis of anorexia nervosa or bulimia, thyroid disorder, glaucoma, or urinary retention • Diagnosis of arrhythmias, serious CV disease or other unstable condition • Prior treatment with bupropion or nortriptyline • Hx of psychoactive drug within 1 wk (2 wks for MAOI or protriptyline & 4 wks for fluoxetine or investigational drug) • Currently taking thyroid meds, cimetidine, quinidine, or other Type 1 antiarrhythmics, guanethidine, bretylium, or other similar antihypertensives • Alcohol/ substance abuse within past yr • Actively suicidal • Pregnant, lactating or unwilling to take contraceptives	**Efficacy** • HAMD • CGI-I • CGI-S • HAMA **Safety** • AEs were coded using a standardized COSTART terms • Vital Signs • Weight • ECGs	• Mean decrease in HAMD scores similar for both groups (47.1% for *Wellbutrin* and 49.7% for nortriptyline) • 22 bupropion patients and 24 nortriptyline patients considered responders based on at least a 50% decrease in HAMD • No significant differences between groups in CGI-I, CGI-S, HAMA, or POMS scores • Most common AEs in bupropion patients: dry mouth, constipation, headache, nausea, insomnia, dizziness • Most common AEs in nortriptyline patients: dry mouth, constipation, dizziness, headache, tachycardia, tremor, somnolence • 10/58 bupropion patients and 6/57 nortriptyline patients withdrew due to AEs • 1 patient in each group had seizure following alcohol consumption
6-wk treatment phase (16)	• Double-blind • Randomized • Multicenter • N=124	***Wellbutrin*** 225-450 mg/day **Trazodone** 150-400 mg/day	**Inclusion Criteria** • Adults (≥18 yrs) with nonpsychotic MDD • 21-item HAMD score ≥20 • Major depressive episode of 2-24 mns duration **Exclusion Criteria** • Predisposition to seizure or taking meds that could lower seizure threshold • Hx or current diagnosis of anorexia nervosa or bulimia, or ventricular arrhythmias • Hx priapism or treated with meds associated with priapism • Any unstable medical condition	**Efficacy** • HAMD • CGI-I • CGI-S • HAMA **Safety** • AEs elicited with a standardized verbal probe • Vital Signs • Weight	• Decrease in HAMD, HAMA, CGI-S significantly greater for trazodone patients at day 7, but similar for both groups at subsequent weeks • Greater improvement in HAMD sleep score noted in trazodone patients at days 7 and 14 • Mean decrease in HAMD scores similar for both groups – *Wellbutrin* 62.3% and trazodone 51.3% • 33 bupropion patients and 21 trazodone patients considered responders based on at least a 50% decrease in HAMD scores • Mean weight change at end of treatment was -2.5 lb for bupropion patients and +1.2 lb for trazodone patients • Greater incidence of anxiety and anorexia in bupropion patients • Greater incidence of somnolence, increased appetite, edema in trazodone patients

Duration	Study Design	Treatments	Inclusion/ Exclusion Criteria	Endpoints	Results
			• Prior treatment with bupropion or trazodone • Hx of psychoactive drug within 1 wk (2 wks for MAOI or protriptyline & 4 wks for fluoxetine or investigational drug) • Currently taking digoxin or phenytoin • Alcohol/ substance abuse within past yr • Actively suicidal • Pregnant, lactating or unwilling to take contraceptives		• 12/62 bupropion patients and 15/60 trazodone patients withdrew due to AEs • 1 patient in the bupropion group had seizure (patient was found to be predisposed)
Up to 13-wk treatment phase (17)	• Double-blind • Randomized • N=147	***Wellbutrin*** 300-450 mg/day **Doxepin** 100-225 mg/day	**Inclusion Criteria** • Adults (≥18 yrs) with nondelusional MDD • Major depressive episode of 1-24 mns duration • Chloral hydrate for insomnia was allowed **Exclusion Criteria** • Dementia • Evidence of seizure disorder • Conditions incompatible with tricyclics • Hx of psychotropic drug within 1 wk (2 wks for MAOI or neuroleptics) • Recent Hx of alcohol or substance abuse • Actively suicidal • Pregnant, lactating or unwilling to take contraceptives	**Efficacy** • HAMD • CGI-I • CGI-S • Zung SDS • HAMA **Safety** • AEs • Vital signs • Weight	• Decrease in HAMD scores significantly greater for doxepin at weeks 2 and 3, but similar during subsequent weeks • Greater improvement in HAMD sleep score noted in doxepin patients • No significant differences between groups in HAMA or SDS scores • At 13 weeks, CGI much improved or very much improved in 62% of bupropion patients and 49% of doxepin patients • Dry mouth, constipation, sedation, and increased appetite reported 2 - 3 times more often in the doxepin group • Most commonly reported AEs in bupropion group: agitation, insomnia, dry mouth, constipation, nausea • Withdrew due to AEs: bupropion (n=8) and doxepin (n=10)
Up to 13-wk treatment phase (18)	• Double-blind • Randomized • Multicenter • N=114	***Wellbutrin*** 300-450 mg/day **Amitriptyline** 75-150 mg/day	**Inclusion Criteria** • Outpatients (18-65 yrs) • Current major depressive episode of 1-24 mns duration • 21-item HAMD score ≥18 **Exclusion Criteria** • Hx of physical illness, schizophrenia, schizoaffective illness, chronic or acute organic brain syndrome, mental deficiency, alcoholism, epilepsy, or drug addiction.	**Efficacy** • HAMD • CGI-I • CGI-S • HAMA • SDS • BDI **Safety** • 35-item treatment-emergent symptom checklist • Vital signs • Laboratory tests • ECG • EEG	• No significant differences between groups in frequency, degree, or rate of response based on HAMD, HAMA, or CGI • At end of active treatment, CGI was much improved or very much improved in 74% with bupropion and 79% with amitriptyline • Anticholinergic and cardiovascular side effects more common in amitriptyline patients • Headache, decreased appetite, nausea/vomiting, and agitation/excitement more common in bupropion patients • Withdrew due to AEs: bupropion (n=3) and amitriptyline (n=1)
6-wk treatment phase (18)	• Double-blind • Randomized • Multicenter • N=92	***Wellbutrin*** 300-750 mg/day **Amitriptyline** 75-225 mg/day	**Inpatients** (18-67 yrs) with similar inclusion/exclusion criteria as presented above	Same as presented above	• No significant differences between treatment groups in frequency, degree, or rate of response based on HAMD, HAMA, and CGI • Unspecified clinically significant AEs were reported in 30 bupropion patients and 29 amitriptyline patients

Duration	Study Design	Treatments	Inclusion/ Exclusion Criteria	Endpoints	Results
					• Withdrew due to AEs: bupropion (n=6) and amitriptyline (n=8) • Doses of *Wellbutrin* higher than those currently recommended
5-wk treatment phase (19)	• Placebo-controlled • Double-blind • Randomized • N=63	***Wellbutrin*** 150 mg/day ***Wellbutrin*** 300-450 mg/day **Imipramine** 25-150 mg/day **Placebo**	**Inclusion Criteria** • Adults (≥55 yrs) with nonpsychotic MDD • Current major depressive episode of 1-24 mns duration • 21-item HAMD score ≥18 **Exclusion Criteria** • Experimental drug within 14 dys • Hx of cerebral vascular accident; severe cardiovascular, renal, or hepatic disease; convulsive disorder; elevated intraocular pressure; obvious psychosis; urinary retention (males) • Abnormality on the SMA-25, thyroid screen, routine urinalysis, CBC, or ECG	**Primary Endpoint** • HAMD **Secondary Endpoints** • CGI-I • CGI-S • HAMA • SDS • SAS • Safety was assessed by adverse event reports	• Significant improvement versus placebo noted for all active groups on HAMD, HAMA, and CGI scores • No significant differences noted between treatment groups on any measure • Incidence of dry mouth, tremor, nervousness, fatigue, loss of libido, and constipation significantly higher in imipramine patients than bupropion patients • Side effects profiles of placebo and bupropion groups were similar • No significant differences in AEs between high- and low-dose bupropion groups

KEY: AEs=adverse events, **CBC**=Complete Blood Count, **CGI**=Clinical Global Impressions Scale (**CGI-I**=Improvement, **CGI-S**=Severity), **ECGs**= electrocardiograms, **CV**=cardiovascular, **EEG**=electroencephalogram, **HAMA**=Hamilton Rating Scale for Anxiety, **HAMD**=Hamilton Rating Scale for Depression, **HRQoL**= Health-related quality of life, **MAOI**=Monoamine Oxidase Inhibitor, **Hx**=History, **MDD**=Major Depressive Disorder, **MEI**=Motivation and Energy Inventory, **mn(s)**=month(s), **POMS**=Profile of Mood States, **SDS**=Self-rating Depression Scale, **SSRIs**=selective serotonin reuptake inhibitors, **wk(s)**=week(s), **yr(s)**=year(s),

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REFERENCES

1. Prescribing Information for *Wellbutrin XL*.
2. Data on file, *Wellbutrin XL*, HM2004/00316/00, Study AK130926 Report Synopsis, 2004.*
3. Data on file, *Wellbutrin XL*, HM2004/00315/02, Study AK130927 Report Synopsis, 2004.*
4. Croft H, Settle E, Houser T, et al. A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline. Clin Ther 1999;12:643-658. AK1A4001*
5. Coleman CC, Cunningham L, Foster V, et al. Sexual dysfunction associated with the treatment of depression: a placebo-controlled comparison of bupropion sustained release and sertraline treatment. Ann Clin Psychiatry 1999;11:205-215. AK1A4002*
6. Kavoussi RJ, Segraves RT, Hughes AR, et al. Double-blind comparison of bupropion sustained release and sertraline in depressed outpatients. J Clin Psychiatry 1997; 58:532-537. 209*
7. Data on file, *Wellbutrin SR,* RM2001/00161/00, Clinical Study Report for Study 209, 2001.
8. Coleman CC, King BR, Bolden-Watson C, et al. A placebo-controlled comparison of the effects on sexual functioning of bupropion sustained release and fluoxetine. Clin Ther 2001;23:1040-1058. AK14007*
9. Data on file, *Wellbutrin SR,* RM2000/00500/00, Study AK1A4006, 2002 pgs 1-19, 27.*
10. Feighner JP, Gardner EA, Johnson JA et al. Double-blind comparison of bupropion and fluoxetine in depressed outpatients. J Clin Psychiatry 1991;52:329-335.*
11. Weihs KL, Settle ED, Batey SR et al. Bupropion sustained-release versus paroxetine for the treatment of depression in the elderly. J Clin Psychiatry 2000;61:196-202.*
12. Nieuwstraten CE, Dolovich LR. Bupropion versus selective serotonin-reuptake inhibitors for treatment of depression. Annals of Pharmacotherapy 2001;35:1608-1613.
13. Thase M, Haight B, Richard N et al. Remission rates following therapy with bupropion or selective serotonin reuptake inhibitors. Poster presented at the 156th Annual Meeting of the American Psychiatric Association; May 17-22, 2003; San Francisco, CA.
14. Data on File, *Wellbutrin SR,* Remission Analysis of studies (4001,4002,4006,4007), 2003.
15. Masco HL, Kiev A, Holloman LC, et al. Safety and efficacy of bupropion and nortriptyline in outpatients with depression. Curr Ther Res Clin Exp 1994; 55:851-863.
16. Weisler RH, Johnston JA, Lineberry CG, et al. Comparison of bupropion and trazodone for the treatment of major depression. J Clin Psychopharmacol 1994; 14:170-179.
17. Feighner J, Hendrickson G, Miller L, et al. Double-blind comparison of doxepin versus bupropion in outpatients with a major depressive disorder. J Clin Psychopharmacol 1986; 6:27-32.
18. Chouinard G. Bupropion and amitriptyline in the treatment of depressed patients. J Clin Psychiatry 1983; 44:121-129.
19. Branconnier RJ, Cole JO, Ghazvinian S, et al. Clinical pharmacology of bupropion and imipramine in elderly depressives. J Clin Psychiatry 1983; 44:130-133.

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